Eptifibatide blocks the increase in C-reactive protein concentration after coronary angioplasty

Álvaro Merino Otermin, Miguel Artaiz Urdaci, Jaume Bergadá García, María Riera Sagrera, Bernat Vidal Salvá and Antonio Rodríguez Fernández

INTRODUCTION

C-reactive protein (CRP) is elevated in patients with stable coronary artery disease demonstrated by angiography, and its serum values increase notably in acute coronary events like unstable angina and acute myocardial infarction. All authors agree that an abrupt increase in inflammatory status leads to an elevation of the markers cited which, in turn, induces the activation of coagulation, thus generating thrombin and increasing intra-arterial thrombosis. Nevertheless, there is the possibility that circulating thrombin, in turn, produces an elevation in inflammatory markers, closing a feedback loop that would explain the high elevation of CRP and cytokines in patients with arterial thrombosis. In this study we evaluated blockade of thrombin generation by means of a glycoprotein (GP) IIb/IIIa receptor (eptifibatide) to determine if it reduces CRP elevation after coronary angioplasty.

PATIENTS AND METHOD

This study is designed prospectively with all the inclusion and exclusion criteria determined previously.
Patients and study design

The study included 31 consecutive patients in which coronary angioplasty was performed in our hemodynamics laboratory. Patients with diseases that could present high CRP values were excluded: inflammatory, infectious, neoplastic, endocrine, and metabolic diseases, recent surgery or acute myocardial infarction (<3 months), patients with angioplasty on a venous graft and angioplasty in acute myocardial infarction.

The patients were included consecutively in both groups. First, 17 patients under treatment were included and then the 14 patients who constituted the control group were included. All patients followed the usual angioplasty protocol of our center. The group of 17 treated patients received a bolus of 180 µg/kg i.v., and a perfusion of eptifibatide 2 µg/kg/min i.v. at the end of angioplasty, immediately after extracting the post-procedure blood sample. The eptifibatide perfusion was maintained for 12 h and was not continued later in order to determine if there was a new increase in CRP as a result of renewed thrombin generation. The control group of 14 patients received conventional treatment.

Laboratory analysis and sample collection

Blood samples were extracted before and after angioplasty, and 6 h, 24 h, and 48 h after the procedure. CRP samples were obtained in biochemistry tubes without coagulant and centrifuged at 2000 (10 min. They were analyzed in our center by nephelometry. The limit of normality was 0.3 mg/dl.

Statistical analysis

The comparison between groups was made using the non-parametric Mann-Whitney test and ANOVA with the Friedman test for comparison of means between groups. The significance level was P<.05.

RESULTS

Both groups were similar in age (control 65.1±10.2 years; eptifibatide 62.7±8.8 years; P=NS), body surface area (1.8±0.18 m² versus 1.95±0.17 m²; P=NS), history of arterial hypertension (42.8% versus 47%; P=NS), smoking habit (21.4% versus 47%; P=NS), and hypercholesterolemia (21.4% versus 29.4%; P=NS). Diabetic patients were excluded. There were no differences in the clinical presentation: 9 of 14 patients in the group control (64.3%) and 9 of 17 patients in the treated group (52.9%) had unstable angina (P=NS). The angiographic characteristics of the lesion also were similar in the two groups. A B2 or C lesion was present in 64.3% of the control group versus 62.5% of the treated patients (P=NS). Lesions with irregular edges were present in 71.4% of controls and 75% of treated patients (P=NS). There were no differences in the severity or final diameter of the lesion measured by quantitative angiography (pre-procedure stenosis: control 82.8±14.1% versus eptifibatide 83.1±11.5%; P=NS) (post-procedure stenosis: control –2.53±8.4% versus eptifibatide –1.7±4.5%; P=NS). The maximum dilatation pressure also was similar (control 18.1±4.1 atm versus eptifibatide 19.5±3.4 atm; P=NS). No patient presented high CK/MB levels after the procedure. CRP values after angioplasty in both groups are shown in Table 1.

DISCUSSION

C-reactive protein and coronary disease

The increase in C-reactive protein values has been related with persistent subclinical instability of the atheroma plaque. CRP elevation in healthy subjects and patients with stable angina is associated with a higher incidence of cardiovascular events.1-10 Patients with unstable angina and elevated CRP present a significant increase in the risk of recurrent ischemia, infarction, and death.5-8 Finally, in coronary angioplasty the atheroma plaque fractures, turning a stable lesion into an unstable one, and C-reactive protein increases, peaking at 24-48 h and normalizing at 72 h.15

Proposed mechanisms of C-reactive protein elevation in coronary artery disease

The current explanation describes CRP elevation in coronary patients or after angioplasty or induction of an «acute inflammatory episode».1-10 Cardiovascular

| TABLE 1. Statistical analysis of C-reactive protein values in the two groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Pre-PTCA        | Post-PTCA       | 6 h             | 24 h            | 48 h            |
| Eptifibatide    | 0.32±0.4 (1.5-0.03) | 0.35±0.42 (1.6-0.03) | 0.43±0.5 (2.1-0.05) | 0.24±0.27 (0.8-0) | 0.57±0.55 (1.61-0) |
| Control         | 0.56±0.57 (2.12-0.1) | 0.53±0.5 (2.0-0.1)  | 1.02±0.89 (3.1-0.41) | 1.34±0.89 (3.76-0.67) | 2.18±2.1 (4.31-0.57) |
| P               | NS              | NS              | <.05            | <.001           | <.05            |

PTCA indicates coronary angioplasty. Values are expressed as mean±standard deviation and, in parenthesis, the range of values.
risk factors induce the secretion of macrophage colony-stimulating factor (MCSF) by the endothelium. The MCSF stimulates the production of more MCSF and IL-1 by the same endothelium and the macrophages of the arterial wall, which favors monocyte adhesion to the endothelium, which, in turn, release cytokines.\textsuperscript{10,12} The macrophages/cytokine-activated monocytes produce large amounts of IL-6 that, when released into the bloodstream, induce the production of CRP by hepatocytes, endothelial cells and macrophages.\textsuperscript{10,12} This could be the mechanism underlying the high MCSF, IL-6, and CRP values in patients with atherosclerosis, but it does not fully explain why these markers are higher in acute coronary syndromes than in stable patients.

We propose that the relation between inflammation and thrombosis is reciprocal. The elevation of CRP, IL-1, and IL-6 has procoagulant effects in general and on the atherosclerotic lesion.\textsuperscript{10,11} CRP also induces the formation of tissue factor by monocytes.\textsuperscript{12} Coagulation is activated by both routes, ultimately leading to thrombin formation in large amounts, and to a very active intra-arterial thrombogenic situation. Thrombin stimulates the release of IL-1 by macrophages,\textsuperscript{13} which in turn induces the production of large amounts of CRP by the macrophages themselves, endothelial cells, and hepatocytes. This would activate the coagulation system again, forming a closed feedback loop between arterial inflammation and thrombosis.

Recent findings support a relation between the activation of coagulation and CRP elevation. Ikonomidis et al studied 40 patients with demonstrated stable coronary artery disease and high CRP (>0.3 mg/dl) and found a mean reduction in CRP levels from 1.25 to 0.23 mg/dl after a month of treatment with 300 mg/day of aspirin.\textsuperscript{10} In a retrospective analysis, abciximab reduced CRP values after angioplasty in a subgroup of patients with unstable angina in the EPIC study.\textsuperscript{16} Finally, in patients with severe sepsis who present an exacerbated inflammatory situation and elevated CRP, a decrease in acute-phase reagents is observed (including CRP) when a thrombin antagonist like antithrombin III is administered.\textsuperscript{17}

**Study design and analysis of results**

The sequence of events in this study were designed to fit as closely as possible the sequence of events that occur in acute coronary syndrome. In first place, we have baseline CRP values. Later, we determined the exact moment of induction of arterial thrombosis by plaque fracture during coronary angioplasty. Since CRP begins to rise 6 h after the stimulus and has a mean life of 19 h, we took blood samples in the previous time intervals.\textsuperscript{15} Next, we administered eptifibatide to the treated group after producing the thrombo-
known effect, it must be concluded that the mechanism by which CRP increases after angioplasty is of a thrombotic type.

REFERENCES